November 20, 2001, the Office included claim 5 among the elected claims for further examination. Accordingly, Applicants had assumed that the Office had granted Applicants' request for rejoinder. Therefore, the presently pending claims should be claims 2-8, 12-22 and 32-37.

In the present Office Action, claims 2-4, 6-8, 12-22 and 32-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Morris et al.* (hereinafter "*Morris*") in view of *Stocker et al.* (hereinafter "*Stocker*"). Specifically, the Office alleges that *Morris* teaches of a regulated antigen delivery system, wherein the plasmid includes a gene encoding a gene product operably linked to a control sequence, an origin of replication conferring vector replication, where the second origin of replication is operably linked to a control sequence that is repressible by a repressor. Furthermore, the Office alleges that *Stocker* teaches of a regulated antigen delivery system wherein the microorganism is a Salmonella species.

Applicants respectfully traverse. According to *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894 (Fed. Cir. 1984), "the critical question, as § 103 makes plain, is whether the invention as a whole would have been obvious to one of ordinary skill in the art at the time it was made". It is improper to compare the prior art with the "gist" of the invention. *Jones v. Hardy,* 727 F.2d 1524, 1527-28 (Fed. Cir. 1984). The MPEP §2143.03 further states that "[t]o establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." It is essential, therefore, to consider all elements of the claimed invention.

Morris, either alone or in combination with *Stocker*, does not teach a regulated antigen delivery system. *Morris* merely teaches a DNA plasmid having the following elements: RepA, one origin of replication ("ori"), copB, copA, a DNA sequence to maintain low copies of the plasmid, a marker, a polylinker, and a termination sequence adjacent to the exogenous DNA to be inserted. Nowhere in the specification does *Morris.* teach the limitations of the present invention. For example, the plasmid in *Morris* does not contain <u>two</u> origin of replications, an element of the present invention. The two origins of replication of the Regulated Antigen Delivery System ("RADS") of the present application serve an important purpose. As described in the specification, the RADS comprises a runaway vector ("RAV") and a repressor operably linked to an

activatible control sequence. DNA polymerase III initiates replication at the first ori, allowing the microorganism to maintain low copies of the RAV, for example, in culture. In the presence of an inducer, such as arabinose, the microorganism cannot make high copies of the RAV because the inducer interacts with the activatible control sequence to activate expression of a repressor. The repressor, in turn, interacts with the first control sequence to prevent utilization of the second origin of replication ("ori") on the RAV. Thus, in the presence of an inducer, the microorganism cannot make high copies of the RAV. In the absence of an inducer, on the other hand, the repressor is not expressed, thereby allowing the microorganism to switch to runaway expression. In short, the two ori's allow the RADS to switch between a maintenance state and a "runaway" state. A DNA plasmid with only one control sequence, as taught in *Morris*, would result in a completely different molecular system from the present invention.

In addition, *Morris* does not implicitly or explicitly suggest insertion of an antigen into the plasmid nor does it suggest delivery of said antigen to a host. It is well-recognized in the art that a mere expression of a DNA sequence in a plasmid will not necessarily elicit an immune response. The present invention, on the other hand, recognizes the importance of a careful, regulated delivery of an antigen to a host's immune system by teaching elements, such as two ori's and control sequences, of the RADS that makes the RADS effective and efficient in eliciting an immune response. The RADS of the claimed invention comprises a RAV that has at least two different ori's. The two different ori's allow the microorganism to switch from low copy to high copy replication and vice versa. (Specification on page 8, lines 12-15, Example 2 on page 50, 11-23, and Figure 1). In the absence of an inducer that causes expression of the repressor, the RADS switch to runaway expression, which allows the RADS to expose a large dose of the vector-encoded foreign gene product to the vertebrate's lymphoid tissue, thereby efficiently eliciting an immune response.

Furthermore, *Morris* teaches away from the present invention. *Morris* criticizes the "runaway" nature of mutant plasmids because they drain the host's energy supply. Because the DNA plasmid described in *Morris* is not an antigen delivery system, runaway expression and therefore, presentation of a large dose of the antigen, is not an advantage. The present invention, on the other hand, recognizes the advantages of the

"runaway" aspect of the RADS. Runaway expression allows presentation of a large dose of the antigen to the host's immune system. Further, the "runaway" aspect of the RADS purposely challenges and ultimately overwhelms the microorganism's capacity for survival. This allows efficient and effective containment of the microorganism after presentation of the antigen. In this way, the microorganism cannot persist in the host and cause an unwanted side effect. Therefore, while *Morris* considers runaway expression as a disadvantage, the present invention takes advantage of runaway expression to efficiently and effectively deliver an antigen.

Stocker, either alone or in combination with *Morris*, also does not teach or suggest a regulated antigen delivery system. *Stocker* focuses on attenuation of the microorganism by introducing non-reverting, non-leaky mutations that block essential biosynthetic pathways in the microorganism. The mutations cause the microorganism to depend on certain nutrients for survival, but which are not available in the host. The present invention, on the other hand, contains the microorganism through runaway expression of the RAV, which not only allows presentation of a large dose of antigen to a host's immune system, but also overwhelms the microorganism's survival capacity. Survival of the microorganism, therefore, depends on careful regulation of the RADS and not on a nutrient requirement as taught by *Stocker*.

In addition, *Stocker* merely mentions that a regulated expression cassette may be introduced into the microorganism. However, *Stocker* does not describe the components of the RADS. *Stocker* does not explicitly or implicitly suggest a regulated antigen delivery system comprising two ori's, activatible control sequences, and/or control sequences that are repressible by repressors. Moreover, *Stocker* does not describe how the components of the expression cassette should be arranged to achieve proper regulation, as in the RADS of the present invention. *Stocker* fails to teach or suggest how regulation of the expression of an antigen can be achieved. Without proper regulation of the expression of the antigen, runaway expression cannot be switched on and off.

Finally, obviousness cannot be established by combining the teachings of the references to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. *ACS Hospital Systems, Inc. v. Montefiore*

Hospital, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed Cir. 1984). There is no explicit or implicit suggestion in either reference to combine them to teach the present invention. As discussed above, each reference alone does not teach or suggest any of the limitations of the present invention. Even in combination, the cited references do not teach every limitation of the present invention. For example, neither reference teaches a RADS with two ori's. Absent the teaching or suggestion of every element or limitation of the claimed invention, the references cannot render obvious the present invention.

In view of the above, Applicants submit that the claimed invention is not obvious. Applicants respectfully request reconsideration and withdrawal of the Office's rejection under 35 U.S.C. § 103(a).

CONCLUSION

In light of the above remarks, Applicants submit that they have overcome or obviated all of the Office's rejections. Applicant believe the application is in proper condition for allowance, and respectfully request that such allowance be granted.

Respectfully submitted,

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